Denervation of Native Kidneys in a Renal Transplant Recipient: One Swallow Does Not Make a Spring

Alexandre Persu,[1,2] Jean-Philippe Lengelé,[2,3] Yu Jin,[4] Nada Kanaan,[5] and Jan A. Staessen[4,6]

Publication of the Symplicity HTN-1[1] and HTN-2[2] trials showed the feasibility of catheter-based renal sympathetic denervation (RDN) in patients with drug-resistant hypertension and unleashed an unprecedented wave of enthusiasm. Advocates of the technique, driven by legions of marketers, proposed numerous potential applications of RDN, including atrial fibrillation, heart failure, metabolic syndrome and diabetes mellitus, obstructive sleep apnea, and even polycystic ovary syndrome. In this issue of the Journal, Portasiewicz and colleagues[3] report the first case of RDN of the native kidneys in a 58-year-old kidney graft recipient. Before the procedure, blood pressure remained uncontrolled despite substitution of cyclosporine with tacrolimus and prescription of 5 antihypertensive drug classes. Renal function was altered, partly because of allograft rejection, with an estimated glomerular filtration rate (eGFR) of 38 ml/min/1.73m^2. Using the Symplicity system, radiofrequency energy was applied at 6 different locations in the right renal artery and at 5 sites in the left renal artery. Twenty-four-hour ambulatory blood pressure decreased by 20/15 mm Hg at 3 months and by 16/12 mm Hg at 6 months, left ventricular mass declined, and antihypertensive drug treatment was tapered to 2 drugs, whereas eGFR remained unchanged (39 ml/min/1.73m^2) at 6 months.

This "first-in-man" case report[3] leaves several questions unanswered. The authors did not report on urinary sodium excretion and therefore did not exclude excessive salt intake, which is a major cause of treatment resistance, especially in patients with chronic kidney disease.[4] Furthermore, one wonders why the Polish investigators did not try using angiotensin-converting enzyme inhibitors, an established blood pressure–lowering treatment in kidney transplant recipients,[5] or use thiazide instead of loop diuretics. Besides stenosis of the artery of the renal graft, other less frequent causes of secondary hypertension in kidney transplant recipients should have been excluded, in particular pheochromocytoma, which can cause resistant hypertension and recurrent hypertensive crises.[6] Finally, the authors did not assess adherence, for instance by measuring drug levels in urine or witnessing drug intake,[7] nor did they use single-pill drug combinations that improve adherence to treatment.

Although the authors must be complimented on bringing their case report to publication, the clinical implications are minimal. The short follow-up of 6 months, the unstandardized method of blood pressure measurement, the absence of a strategy to taper antihypertensive drug treatment after the procedure, and the lack of imaging of the native kidneys at 6 months hamper the extrapolation of the case report to clinical practice.

It has been suggested that the RDN might be particularly efficient in patients with chronic kidney disease because this condition is characterized by inappropriate sympathetic activation and because afferent denervation in animal models of chronic kidney disease produced promising results.[8] Several authors also highlighted the potential interest of RDN in renal transplant recipients.[9] Indeed, in this population, hypertension is frequent, often treatment resistant, and associated with deterioration of the graft function.[5] Although the renal transplant itself is denervated, the native kidneys may still cause activation of the sympathetic nervous system through afferent signaling, thereby contributing to the maintenance of high blood pressure.[5] Previous studies in kidney transplant recipients[10] showed a decrease in peripheral arterial

Correspondence: Alexandre Persu (alexander.persu@uclouvain.be).

Initially submitted March 8, 2014; date of first revision March 18, 2014; accepted for publication March 19, 2014; online publication May 2, 2014.

[1]Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium; [2]Division of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [3]Nephrology Department, Grand Hôpital de Charleroi, Gilly, Belgium; [4]Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium; [5]Division of Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [6]Department of Epidemiology, Maastricht University, Maastricht, The Netherlands.

doi:10.1093/ajh/hpu075

resistance and blood pressure after nephrectomy of the native kidneys, likely because of normalization of sympathetic nervous activity.[11] Furthermore, altered renal function and hypertension triggered by immunosuppressive drugs, in particular cyclosporine, are at least partly mediated by increased sympathetic tone.[5] Inhibition of the sympathetic nervous system may thus counteract several pathways contributing to post-transplant hypertension. However, the enthusiasm for this potential new application of RDN should be viewed within the context of potential procedural pitfalls linked to progressive shrinking of arteries of the native kidneys, low renal plasma flow, the difficulty to perform a complete denervation, and the increased risk of spasm and vascular damage.[12] A report by Schlaich and colleagues illustrated the soundness of these concerns.[12] These investigators attempted to perform RDN in 12 patients with end-stage renal disease and uncontrolled blood pressure. Three patients were deemed ineligible because of dual renal arteries (n = 1) or renal artery diameters of <4 mm at both sides (n = 2). Furthermore, in 2 of 9 patients who underwent RDN, the 2-minute ablation periods were prematurely aborted on 3 occasions because of rapidly rising temperature levels, most likely because of the lack of cooling by the reduced renal blood flow. Also, despite the theoretical interest of RDN in patients with chronic kidney disease,[8] renal dysfunction at baseline may negatively influence the outcome. Indeed, in the European Network COordinating research on Renal Denervation (ENCOReD) registry, lower eGFR predicted a decreased likelihood of a favorable blood pressure response to RDN.[13]

In conclusion, one swallow does not make a spring. A single case of successful RDN in a kidney graft recipient is nothing more than a hypothesis-generating observation and should certainly not be considered as an incentive to perform RDN in transplanted patients outside the framework of randomized clinical trials. Several factors, including age, duration of hypertension, time elapsed since end-stage renal disease, and transplantation, may all affect the technical feasibility, the blood pressure response, and the renal outcomes of RDN in this particular patient group. On 9 January 2014, Medtronic announced that Symplicity HTN-3[14] failed to meet its primary efficacy endpoint (http://www.tctmd.com/show.aspx?id=123265), which was defined as baseline-adjusted between-group difference in office systolic blood pressure of ≥5 mm Hg. Symplicity HTN-3[14] is a randomized trial including 535 resistant hypertensive patients randomized to RDN or control (sham) in a ratio of 2:1, with the goal to evaluate the efficacy and safety of RDN in treatment of resistant hypertension. The failure of Symplicity HTN-3 to reach its primary efficacy endpoint[15] shows the gap between expectations raised by case reports and small uncontrolled observational studies and results produced by a rigorous study with blinded endpoint assessment. It implies that even in resistant hypertensive patients with fewer comorbidities and a less complex underlying disease process than kidney transplant recipients, RDN cannot be applied in routine clinical practice, but only within the context of clinical research. Overoptimistic views have been abandoned, and the results of randomized controlled trials devoted to the efficacy and safety of RDN in renal transplants recipients (ISAR-HTN; NCT 01899456) are still awaited.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373:1275–1281.
2. Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; 376:1903–1909.
3. Protasiewicz M, Poczatek K, Banasik M, Poreba R, Podgorski M, Kurcz J, Mysiak A, Klinger M, Boratynska M. Successful renal artery denervation in a renal transplant recipient with refractory hypertension. *Am J Hypertens* 2014; 27:982–984.
4. De NL, Minutolo R, Bellizzi V, Zoccali C, Cianciaruso B, Andreucci VE, Fuiano G, Conte G. Achievement of target blood pressure levels in chronic kidney disease: a salty question? *Am J Kidney Dis* 2004; 43:782–795.
5. Chatzikyrkou C, Menne J, Gwinner W, Schmidt BM, Lehner F, Blume C, Schwarz A, Haller H, Schiffer M. Pathogenesis and management of hypertension after kidney transplantation. *J Hypertens* 2011; 29:2283–2294.
6. Kanaan N, Persu A, Van IG, Malaise J, Goffin E. Recurrent pulmonary oedema and severe hypertension after renal transplantation: other reasons than renal artery stenosis. *Nephrol Dial Transplant* 2008; 23:397–399.
7. Fadl-Elmula IM, Hoffmann P, Fossum E, Brekke M, Gjønnæss E, Hjørnholm U, Kjær V, Rostrup M, Kjeldsen SE, Os I, Stenehjem A, Høieggen A. Renal sympathetic denervation in patients with treatment-resitant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. *Hypertension* 2013; 62:526–532.
8. Blankestijn PJ, Joles JA. Hypertension: Renal denervation in chronic kidney disease. *Nat Rev Nephrol* 2012; 8:439–440.
9. Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension. Novel implications for an old concept. *Hypertension* 2009; 54:1195–1201.
10. Curtis JJ, Luke RG, Diethelm AG, Whelchel JD, Jones P. Benefits of removal of native kidneys in hypertension after renal transplantation. *Lancet* 1985; 2:739–742.
11. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, Dietl KH, Rahn KH. Sympathetic nerve activity in end-stage renal disease. *Circulation* 2002; 106:1974–1979.
12. Schlaich MP, Bart B, Hering D, Walton A, Marusic P, Mahfoud F, Bohm M, Lambert EA, Krum H, Sobotka PA, Schmieder RE, Ika-Sari C, Eikelis N, Straznicky N, Lambert GW, *et al.* Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. *Int J Cardiol* 2013; 168:2214–2220.
13. Persu A, Jin Y, Azizi M, Baelen M, Volz S, Elvan A, Severino F, Rosa J, Adiyaman A, Fadl Elmula FE, Taylor A, Pechere-Bertschi A, Wuerzner G, Jokhaji F, Kahan T, *et al.* Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens* 2014; 28:150–156.
14. Kandzari DE, Bhatt DL, Sobotka PA, O'Neill WW, Esler M, Flack JM, Katzen BT, Leon MB, Massaro JM, Negoita M, Oparil S, Rocha-Singh K, Straley C, Townsend RR, Bakris G. Catheter-based renal denervation for resistant hypertension: rationale and design of the SYMPLICITY HTN-3 trial. *Clin Cardiol* 2012; 35:528–535.
15. Staessen JA, Jin Y, Persu A: SYMPLICITY HTN-3 results to be announced: a mystery or a story foretold? *J Biomed Res* 2014; 28:73–74.